UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

MEMORANDUM

Date: 10-OCT-2017

SUBJECT: Ametryn. Review and Generation of Data Evaluation Record

PC Code: 080801
Decision No.: 530423
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0057663
MRID No.: See Table

DP Barcode: D444015
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 834-12-8
40 CFR: 180.222

FROM: Connor Williams, Toxicologist
Risk Assessment Branch 1 (RAB1)
Health Effects Division (HED; 7509P)

THROUGH: Christine L. Olinger,
Chief, Acting RAB1
HED (7509P)

TO: Sarah L. Levy, Chemist
RAB1, HED (7509P)

I. CONCLUSIONS

Updated data evaluation record (DERs) reflecting current HED policies and practices have been provided for the rat 90-day oral toxicity, rat combined chronic toxicity/carcinogenicity and rabbit dermal toxicity studies.

II. ACTION REQUESTED

Update DERs for the ametryn 90-day oral, chronic toxicity/carcinogenicity and dermal toxicity studies as shown below.

MRID Summary Table

Study Type	MRID	Comments
870.3200 21/28-Day Dermal - Rabbit	41067902	Revised DER, Root TXR No. 0052157
870.3100 90-Day Oral Toxicity- Rat	46467501	Revised DER, Root TXR No. 0053261
870.4300 Combined Chronic Toxicity/Carcinogenicity - Rat	40349906	Revised DER, Root TXR No. 0052157

EPA Reviewer: Connor Williams, MHS **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 11/30/17
EPA Secondary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 11/30/17

Template version 03/12

TXR#: 0057663

DATA EVALUATION RECORD – Supplemental
See Original DER – TXR# 0052157

STUDY TYPE: 21-Day Dermal Toxicity – [*Rabbit*]
OPPTS 870.3200 [§82-2]; OECD 416.

PC CODE: 080801 **DP BARCODE:** D444015

TEST MATERIAL (PURITY): Ametryn Technical – 97.4%

SYNONYMS: N^2-ethyl-N^4-isopropyl-6-methylthio-1,3,5-triazine-2,4-diamine (IUPAC); Ametrex; A 1093; Ametryne; carbamic acid, methyl-, o-isopropoxyphenyl ester; Crisatrine; Evik; G-34162; Gesapax.

CITATION: Huber, K.R. (1989) 21-Day dermal toxicity study in rabbits. CIBA-GEIGY Corporation, 556 Morris Ave., Summit, New Jersey 07901. Laboratory study number: 882215. February 3, 1989. MRID 41067902. Unpublished.

SPONSOR: Agricultural Division, Ciba-Geigy Corporation, Greensboro, NC 27419

EXECUTIVE SUMMARY:

In a 21-day dermal toxicity study (1989, MR.ID 41067902), Ametryn® (97.4% a.i., batch/lot# FL 840991) was applied to the shaved skin of 5 approximately 14-15 week old New Zealand white rabbits/sex/dose at dose levels of 0, 10, 100, or 1000 mg/kg bw/day, 6 hours/day for 21 - 24 days. Clinical signs, motor activity, functional observational battery, changes in body weights, food consumption, hematological and clinical chemical parameters, organ weight changes, necropsy and histopathological changes were all examined.

Shortly before the first application, and as needed thereafter, the fur of each animal was clipped from the flank and dorsal area of the trunk over an area of at least 10% of the total body surface area. The applied quantities of test material were adjusted weekly to individual animal body weight. The substance was moistened with sterile water and applied to the intact skin of the clipped area. A gauze dressing was applied over the test site and secured with veterinary adhesive wrapping. Following dosing, a fitted Elizabethan collar was applied to each animal. The dressings were removed after 6 hours and the application sites were cleaned with tap water and dried with paper towel. Rats in the control group were treated similarly but with sterile water only.

There were no treatment-related effects observed for changes in absolute bodyweight, bodyweight gain or food consumption in either sex when compared to control animals. No other treatment-related effects were observed.

Therefore, the systemic NOAEL is 1000 mg/kg/day as no adverse effects were observed. The dermal LOAEL could not be established.

This 21-day dermal toxicity study in the rabbit is **Acceptable/Non-Guideline** and does not satisfy the guideline requirement (OPPTS 870.3200; OECD 410). The limiting factor is that there were only 5 rabbits/sex/dose limiting the interpretation of the body weight and organ weight differences and histopathology was limited and incomplete.

COMMENTS:

This revised Executive Summary alters the conclusions of the previous review. The NOAEL/LOAEL values have been updated to reflect current practices in hazard evaluation.

Previously, the LOAEL was set based on decreases in bodyweight gain and food consumption in both sexes. However, according to current HED standards and practices, decreases in bodyweight gain without a corresponding decrease in absolute body weight are not considered to be adverse.

The previous DER also noted the following:
There were minimal decreases in the indicators of circulating red cell mass (RBCs, HGB, and HCT) among treated groups. Dose-related increases in cholesterol, triglycerides, and GGT (statistically significant) were also observed in high-dose males. Absolute hepatic weights were statistically increased in the low- and high-dose females, but there was not a clear dose-response and no histopathological correlation. Apparent increases in absolute spleen weights in males (+1 to 6%) and in relative (to body weight) spleen weights (+2 to 14%) in females suggested a possible mild effect of treatment on the spleen. Mild, dose-related increases in absolute cardiac weights in males (+2 to 8%) suggested a possible effect on the heart. Apparent decreases in absolute and relative prostate weights (-20 to 22%) at all dose levels, and reductions in testicular weights in the mid- (-12%, absolute and -5% relative) and high- (-20%, both absolute and relative) dose males were suggestive of possible effects.

However, none of the blood effects or organ weight differences were associated with gross lesions and in the mid-dose group specifically are not considered to be statistically related to treatment. As a result, none of the effects observed in blood or organ weight changes are considered to be adverse under current HED standards and practices. As a result, the NOAEL has been updated for both sexes to the highest dose tested of 1000 mg/kg/day. The LOAEL could not be established in this study.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

EPA Reviewer: Connor Williams, MHS
OPP, Health Effects Division (7509P)
EPA Secondary Reviewer: Sarah S. Gallagher, Ph.D.
OPP, Health Effects Division (7509P)

Signature:
Date: 12/14/17
Signature:
Date: 12/14/17
Template version 03/12

TXR#: 0057663

DATA EVALUATION RECORD – Supplemental
See Original DER – TXR# 0053261

STUDY TYPE: 90-Day Oral Toxicity – [*Rat*]
OPPTS 870.3100a [§82-1a]; OECD 416.

PC CODE: 080801 **DP BARCODE:** D444015

TEST MATERIAL (PURITY): Ametryn (97.2% a.i.)

SYNONYMS: G34162 technical; 2-(ethylamino)-4-isopropylamino-6-methyl-thio-s-triazine

CITATION: Bachmann, M. (1998) Ametryn (G34162 tech.): 3-Month oral toxicity study in rats (administration in food). Novartis Crop Protection AG, Stein, Switzerland. Laboratory Study ID: 961100, January 12, 1998. MRID 46467501. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Rd., P.O. Box 18300, Greensboro, NC

EXECUTIVE SUMMARY:

In a subchronic oral toxicity study (1998, MRID 46467501), Ametryn (97.2% a.i., Batch #: FL920248) was administered to 10 Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 25, 100, 500, or 2000 ppm (equivalent to 0/0, 1.9/2.0, 7.4/7.6, 36.1/36.2, and 146.3/139.5 mg/kg/day [M/F]) for 90 days. An additional 10 rats/sex were treated at 0 or 2000 ppm for 90 days, and then were allowed a recovery period of 4 weeks.

No effects were observed on mortality or clinical signs. There were no treatment-related adverse effects on hematology, clinical chemistry, urinalysis, or histopathology for either sex. At 2000 ppm, the following treatment-related findings ($p<0.01$ unless otherwise indicated) were observed: (i) absolute body weight was decreased in both sexes (22% for males; 13% for females); (ii) cumulative body weight gains were decreased in both sexes (30% for males; 23% for females); (iii) food consumption showed a negative trend ($p<0.05$) and was decreased (not statistically significant; NS) by 13-30% in both sexes throughout the treatment period; (iv) overall food consumption (calculated by reviewers) was decreased by 19-20% in both sexes; (v) food consumption ratios were transiently decreased (no statistics performed; NSP) in the males (decreased 24%, Week 1) and females (decreased 8-27%, Weeks 1-6); and (vi) water consumption was decreased by 8% in the males. In the 2000 ppm recovery groups, there were compensatory increases in food consumption, food consumption ratio, and water consumption (males only). After the 4-week recovery period, the mean absolute body weights remained decreased for the

2000 ppm groups as compared to controls (12% for the males; 7% for the females), but showed signs of recovery. A number of absolute organ weights were decreased for the high dose animals; however, there were no corroborative gross or histopathological effects, so the changes were considered to be associated with the decreased absolute body weights.

The LOAEL is 2000 ppm (equivalent to 146.3/139.5 mg/kg/day [M/F]) based on decreased absolute body weight in both sexes. The NOAEL is 500 ppm (equivalent to 36.1/36.2 mg/kg/day [M/F]).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat.

COMMENTS:

This revised Executive Summary alters the conclusions of the previous review. The NOAEL/LOAEL values have been updated to reflect current practices in hazard evaluation.

Previously, the LOAEL was set at 500 ppm (36.1/36.2 mg/kg/day [M/F]) based on decreased absolute body weight, body weight gain, and food consumption in both sexes and increased prothrombin time and alkaline phosphatase activity in females. However, reanalysis of the data allowed the reviewers to determine that the changes in prothrombin time and alkaline phosphatase activity were minimal for females at 500 and 2000 ppm and there were no corresponding histopathological findings. As a result, these effects are no longer believed to be appropriate for setting an endpoint. Therefore, these parameters were removed from the LOAEL statement. In addition, the previously noted decreases in absolute body weight in the 500 ppm dose group is no longer considered adverse according to current HED practices. As a result, the LOAEL value is 2000 ppm (146.3/139.5 mg/kg/day [M/F]) based on decreased absolute bodyweight in both sexes. The NOAEL is 500 ppm (36.1/36.2 mg/kg/day [M/F]).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

EPA Reviewer: Connor Williams, MHS **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 12/12/17
EPA Secondary Reviewer: Anwar Dunbar, Ph.D. **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 12-12-17

Template version 03/12

TXR#: 0057663

DATA EVALUATION RECORD – Supplemental
See Original DER – TXR# 0052157

STUDY TYPE: Combined Chronic Toxicity/Carcinogenicity Feeding – [*Rat*] OPPTS 870.4300 [§83-5]; OECD 453.

PC CODE: 080801 **DP BARCODE:** D444015

TEST MATERIAL (PURITY): Ametryn (98.6% a.i.) (MRID 40349905)

SYNONYMS: N^2-ethyl-N^4-isopropyl-6-methylthio-1,3,5-triazine-2,4-diamine (IUPAC); Ametrex; A 1093; Ametryne; carbamic acid, methyl-, o-isopropoxyphenyl ester; Crisatrine; Evik; G-34162; Gesapax.

CITATION: Hazelette, J. and J. Green (1987) Ametryn: Combined chronic toxicity/oncogenicity study in rats. ClBA-GEIGY Corporation, Research Department, Pharmaceutical Division, Summit, New Jersey. Laboratory Report No. 842119. August 24, 1987. MRID 40349906. Unpublished.

Hazelette, J. and J. Green (1987) Ametryn: Supplement to combined chronic toxicity/oncogenicity study in rats. ClBA-GEIGY Corporation, Research Department, Pharmaceutical Division, Summit, New Jersey. Laboratory Report No. 842119. August 24, 1987. MRID 41184201. Unpublished.

SPONSOR: Agricultural Division, Ciba-Geigy Corporation, Greensboro, NC 27419

EXECUTIVE SUMMARY:

In a combined chronic toxicity/carcinogenicity study (MRID# 40349906), Ametryn (98.6% a.i., FL 840991) was administered to groups of 70 Sprague-Dawley [Crl:COBS®CD® (SD)BR] rats/sex at concentrations of 0, 50, or 500 ppm for 104 weeks. This is equivalent to a dose of 0, 2.0/2.5, 20.9/26.2, or 145.3/176.1 mg/kg bw/day [M/F]. Groups of 70 rats per sex received a 5000-ppm diet that was reduced to 4000 ppm after 141 days, and finally further reduced to 2000 ppm after 239 days because of excessive reductions in body weight gain at the higher doses. Ten rats/sex/group were dosed for 52 weeks for interim evaluation, and ten rats/sex/group in the control and the high-dose groups were dosed for 56 weeks followed by a control diet for 4 weeks to assess recovery.

Treatment related effects were noted in the high-dose group (5000/4000/2000 ppm). In terms of mortality, 80% of males and 69% of females in the high-dose group survived to study termination compared with only 43% and 44% of controls. The only treatment-related clinical sign noted was loose feces observed in high-dose males during the time they were fed the 5000-ppm diet. High-dose males weighed 29-48% less than controls when fed the 5000-ppm diet and 18-26% less when

fed the 4000-ppm and by the 2000-ppm diets. High-dose females showed consistent absolute body weight loss relative to controls of between 20% - 34%, regardless of the concentration of test material in the diet. When fed the 5000-ppm diet, high-dose males and females had absolute body weight losses of 20% and 57% respectively relative to controls. When fed the 4000-ppm diet, high-dose males and females had absolute body weight losses of 29% and 15% respectively, relative to controls when fed the 2000-ppm diet for the remainder of the first year.

During the second year, high-dose males gained two times more weight than controls and high-dose females gained 51 % less weight than controls. High-dose males and females consumed 18-41% and 30-45% less food when fed the 5000-ppm diet, 12-17% and 18-22% less when fed the 4000-ppm diet, and 6-14% and 7-12% less when fed the 2000-ppm diet up to day 560 and 532, respectively. Food efficiency for the first 91 days was reduced by 22% and 17% for high-dose males and females, respectively. No toxicologically significant effects were observed on hematology or clinical chemistry parameters except for elevated alkaline phosphatase (68-94% increase) in high-dose females. The 500 ppm and 50 ppm dose groups did not show statistical differences from the control animals.

Males had significantly increased incidences of mineralization/concretions in the renal pelvis (25/70 vs 10/70 for controls), pituitary hyperplasia (26/70 vs. 13/70 for controls), and interstitial cell hyperplasia in the testes (12/70 vs. 2/70 for controls). Males and females had significant increases in the incidence of hepatocellular hyperplasia (males: 34/70 vs. 22/70; females: 36/70 vs. 18/70) and a non-significant increase in the incidence of acinar cell metaplasia (hepatocyte-like cells) in the pancreas (3/70 for males, 4/69 for females vs. 0/70 for controls in both sexes). Females had a significantly increased incidence of "hepatocellular alterations" (49/70 vs. 19/70 for controls) including an increased number of foci of hepatocyte-like cells. Acinar metaplasia in both sexes, interstitial cell hyperplasia in the testes, and hepatocellular alterations in females were observed in the high-dose groups after only 1 year of treatment. The incidences of lesions after 1 year were reduced after the 4-week recovery period.

The LOAEL is 5000/4000/2000 ppm (145.3 and 176.1 mg/kg/day for males and females, respectively) based on decreased absolute body weight in both sexes and histopathologic lesions in the kidney, testes, and pituitary in male rats and in the liver and pancreas both sexes. The NOAEL is 500 ppm (20.9 and 26.2 mg/kg/day, for males and females, respectively).

The incidences of interstitial cell tumors in the testes and epididymal mesothelioma were 9/70 (12.9%, p=0.06) and 3/70 (4.3%, N.S.) in high-dose male rats compared with 3/70 (4.3%) and 0/70, respectively, for controls. The incidence of both lesions exceeded that of historical controls reported in the concurrent study (8.8% and 0%, respectively) and the incidence of interstitial cell tumors in the testes exceeded that reported in 200 l by Charles River Laboratories (CRL) for Sprague-Dawley rats. The incidences of other neoplasms were 4/70 (5.7%, p=0.06) for thyroid follicular cell adenocarcinoma in high-dose males compared with 0/70 for controls, 4/70 (5.7%, N.S.) for hepatocellular adenoma in high-dose females compared with 1/70 (1.4%) for controls, and 24/70 (34.3%, p<0.01) for mammary adenocarcinoma in high-dose females compared with 11/70 (15.7%) for controls; these incidences in the treated rats were above the historical control incidences reported in the current study but were less than the range for spontaneous incidences reported by CRL.

The increased incidences of neoplasms observed in the high-dose group were evaluated by the Cancer Assessment Review Committee (CARC) of HED and it was determined that based on large reduced body weight and weight gain in both sexes in the high-dose animals, the dosage was excessive until study Day 239 when it was reduced to 2000 ppm. The CARC therefore determined

that while the neoplastic findings in the high-dose group cannot be eliminated as a possible line of evidence, they cannot be reliably used for determination of carcinogenic risk. The next lower dose level of 500 ppm was determined by the CARC to be insufficiently high to adequately challenge the animals for carcinogenicity evaluation.

This chronic toxicity aspect of this study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity study [OPPTS 870.4100a]. The carcinogenicity aspect of this study is classified as **Acceptable/Non-Guideline** and satisfies the requirement for a carcinogenicity study (OPPTS 870.4200) in rats.

COMMENTS:

This revised Executive Summary alters the conclusions of the previous review.

Previously, the CARC had determined that the neoplastic findings in the high-dose group could not be considered reliable and that the dose level in the entirety of the study was excessive based on high levels of absolute bodyweight loss observed. The CARC also previously considered the carcinogenic parts of the study to be "Unacceptable/Guideline" based on these determinations.

The most recent meeting of the CARC for ametryn found that while the dosage given to the high-dose animals was considered excessive for the first year, once the dose was reduced to 2000 ppm on day 239 the animals began to stabilize and were no longer considered to be above the Maximum Tolerated Dose (MTD). As a result, the carcinogenic findings in the high-dose animals cannot be ruled out entirely although it is still true that they cannot be used to measure or quantify carcinogenic risk. Based on these new determinations, the CARC now considers the carcinogenic aspects of this study to be "Acceptable/Non-Guideline".

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.